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PRIMARY LANGERHANS CELL HISTIOCYTOSIS OF THE PARIETO OCCIPETAL LOBE.

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Brain involvement by histiocytosis X or Langerhans cell histiocytosis has been well documented in multisystem disease with hypothalamus involvement, although more rare as unifocal hypothalamic involvement.Solitary lobar involvement is a unifocal rare event and only few cases have been reported,mainly as frontal or temporal masses.

We studied a 3 years old girl She consulted because of convulsion crisis.A cortico subcortical 3 cm round lesion in the left parieto occipital carrefour ,hipointense in T1 with a central cystic area.Annular enhancement was observed with gadolinium and there was perilesional oedema with no mass effect.On 3-1-95 surgery has been performed: and a 2.5 cm. yellowish mass has been obtained,with clear cortical limits, but not so clear in depth. Histological examination showed a nodular proliferation diffuse and perivascular in V.Robin spaces of large and irregular cells with indented or convoluted nuclei and bi or multilobulated cells, some giant multinucleated cells with bizarre nucleus intermingled with diffuse astroglial hyperplasia.Foamy histiocytic cells were present in small agregates with focal perivascular lymphocytes.Proliferation markers showed a relatively high kinetic index.Six months later, because of recurrence in MRI a second surgery has been performed.Multiple small yellowish fragments firm in consistency were obtained.Microscopically there were nodules consisting in characteristic Langerhans cells with large folded or indented nuclei with few plasma cells and focal accumulation of eosinophils.Foamy histiocytes were also observed in focal aggregates as well as a few multinucleated cells.A prominent astrocytic hyperplasia was evident in the surrounding brain .Langerhans cells were S-100 and Peanut Agglutinin positive.No necrosis, mitosis nor endothelial vascular hyperplasia could be observed.Birbeck granules were identified in the Langerhans cells at EM.Radiotherapy has been performed and there are no signs of residual/recurrent disease.

DENDRITIC HISTIOCYTOSIS OF THE CENTRAL NERVOUS SYSTEM

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Little is known of the pathogenesis of dendritic histiocytosis of the central nervous system (CNS), epitomized by Langerhans cell histiocytosis (LCH). The pathology of LCH neurological disease is complex. An autopsy on a child with extensive brain disease provided an opportunity for detailed pathological studies and correlation of findings with clinical and imaging data. A 5 year old boy, with a 4 year history of idiopathic thyroid and lung disease presented with neurological signs and symptoms associated with extensive lesions of the brain on MRI that resembled those described in LCH neurological disease. Serial MRIs indicated that some Type 1 lesions abated simultaneously as new ones evolved while Type 2 lesions only progressed during the course of steady deterioration ending in death from acute hydrocephalus 5 months after presentation. Autopsy revealed non-cohesive collections of dendritic histiocytes in lung, thyroid and renal pelvis. There was mild chronic interstitial pneumonia with fibrosis and cystic alteration. Four distinct types of CNS lesions were seen: [1] large and small histiocytic tumors corresponded to Type 2 MRI changes, [2] separate flagrant astrocytic gliosis and [3] gliotic lesions containing histiocytes correlated with Type 1 alterations and [4] perivascular cuffs of only T-lymphocytes. The thickened pituitary stalk, posterior and anterior pituitary were involved by histiocytes. The histology of LCH was lacking in all areas and lesional histiocytes were CD1a, Factor XIIIa, CD68, HLA-DR and vimentin+ but were devoid of Langerhans cell granules. Only those histiocytes in the renal pelvis were strongly S100+. Those in lung were only weakly S-100+. Double staining immunohistochemistry revealed that the CD1a+ CNS histiocytes produced IL-3, IL-5 and less IL-7 and IL-10. Cells did not survive in culture in spite of the use of growth factors. This disorder, that resembled LCH clinically, seems to represent one in which the lesional histiocytes had phenotypic features of both the Langerhans cell and dermal dendrocyte lines, two cell types observed in-vitro when CD34− hemostem cells are cultured with GM-CSF & TNF alpha but, they were S100 negative. Astroglial lesions without a histiocytic component were unstable and corresponded to the Type 1 MRI changes. The astrocytic lesions, the autonomy of these changes and the perivascular T-lymphocyte cuffs suggest a reactive process separate from the collections of histiocytes that formed histiocytomas and Type 2 MRI alterations throughout this brain. This case depicts the complexity of histiocytic disorders and CNS lesions and it illustrates that sharp distinction between maladies featuring Langerhans cells and other dendritic cells may not always be evident.

ARE DYNAMIC ENDOCRINE TESTS USEFUL IN PREDICTING HORMONE DEFICIENCY DURING CHILDHOOD LCH?

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Patients with Langerhans cell histiocytosis (LCH) are at risk for developing late endocrine dysfunction. Common deficits involve AVP and GH and, less frequently, the thyroid, adrenal, and gonadal functions.

Patients and methods - 17 pts, 5 males, median age 8 yrs, range 2.5 to 20 yrs; median age at LCH diagnosis was 5 yrs (range 2 mos -20 yrs). None was on LCH directed therapy. GH deficiency was diagnosed according to current criteria. Dynamic tests including GHRH, TRH, CRF and GnRH were performed in 15/17 pts. Posterior pituitary function was studied by short dehydration test of 7 hrs, and hypertonic 3% saline infusion (0.1 ml/kg/min). GH, TSH, ACTH, cortisol, FSH, LH were determined at times included between 0, 15, 30, 45, 60, 90 and 120 min. T3, T4, FT3, FT4, were measured at time 0. Sodium and AVP, plasma and urine osmolality were also collected at 0, 2, 4, 6, 7 hrs during dehydration test and at 0, 30, 60, 90, 120 min after hypertonic saline infusion. MR of the hypothalamic pituitary area was performed

Results - 9/17 (53%) pts showed normal growth and normal hypothalamic-pituitary, thyroid, adrenal axis, while 8 had endocrine dysfunction. Seven pts had developed DI after a median time of 11 months from the diagnosis (range 6-36 months) and are on DDAVP therapy. Posterior pituitary hyperintensity was absent in all pts with DI; the stalk was thick in 7 (3 without DI). Seven had GH deficiency (with one additional case with a pending diagnosis) after a median time of 56 months (range 13-76 months) from the diagnosis and are on

GH therapy; late thyroid defect was seen and corrected in one patient, and one had untreated hypogonadism. Peak GH response to GHRH was 2-23 (median 9.1) ng/ml in the 7 pts with GH deficiency vs 15.7-36.5 (median 22.5) ng/ml in the others; 3/7 DI pts had blunted TSH response to TRH, including one who developed TSH deficiency 11 yrs after DI. RH were not able to identify occult hormone deficiency in the remaining pts. Dehydration and saline infusion tests were normal in all patents with no DI, regardless of the stalk status.

Conclusion - Blunted GH and TSH response to GHRH and TRH heralds late hormone defect. Short dehydration test and hypertonic saline are not able to identify AVP deficiency even in the presence of stalk infiltration. Dynamic tests seem usefulf for evaluation of anterior pituitary disorders but not for posterior pituitary failure.

PULMONARY INVOLVEMENT IN MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS (MS-LCH). Results from the LCH-I Study.

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Pulmonary LCH in pediatric patients (pts) is a rare event, usually occurring in MS disease. In the international cooperative clinical trial LCH-I 480 pts with LCH were registered. Only 1/283 (0,4%) pts with single system disease had primary lung involvement. In 40/125 MS-LCH (32%) pulmonary involvement (PI) was diagnosed, in 32/40 (80%) at initial presentation and in 8 pts (20%) during follow up investigations. All 125 pts with MS-LCH were treated with monotherapy according to the study protocol and were randomized either to Vinblastin (n=64) or VP-16 (n= 61). 21/40 pts with PI were assigned to the Vinblastin arm and 19/40 to the VP-16 arm. They were 29 male and 11 female (ratio 2,6:1), age at diagnosis ranged from 1m to 14y 6m (median 11m). In 33/40 pts (82%) the diagnosis of PI was documented by x-ray or computed tomography. In 20/40 pts (50%) clinical symptoms, such as cough, tachypnea, dyspnea or chest pain were reported. In 10 pts pulmonary function tests were performed and revealed abnormalities in 4/10 pts. Pathological confirmation of PI was available in 7/40 pts (BAL n=3, biopsy n=4). PI was most often combined with involvement of skin (87%), bone (72%), liver (57%), hematopoiesis (55%) and spleen (50%). Combination of liver involvement and PI occured in 23/125 MS-pts (18%). After 6 weeks of initial treatment 17/40 pts (42%) with PI showed a response and 11/40 pts (28%) a progression of the disease, in another 11 pts the disease state was intermediate. 16/40 pts (38%) with PI died, related to the initial response there were 8/11 fatalities in nonresponders (73%) as opposed to 3/19 (18%) in responders or 4/11 (30%) in intermediate pts. After a median observation time of 1y 3m (1m - 4y 9m) the probability of survival (pSU) was 76% for the whole study population. In pts with PI pSU was 55% versus 85% in pts without PI. The worst prognosis was found in pts with a combination of LI and PI (pSU=33%). 11/15 fatalities had concomitant liver disease (73%) at the time of their death. 12/15 (87%) died with persistent lung disease. Reactivations were reported in 9/40 pts with PI, occurring predominantly in bone in 8/9 pts, 3/9 pts reactivated in the lungs. 14/25 (56%) survivors were free of disease at the last evaluation. 11/25 (44%) pts had active disease, including 4/11 with persistent PI. Drabetes insipidus (DI) developed as a permanent consequence (pc) in 5/40 pts, in 1 pt DI was already present at dx. Lung fibrosis was documented in 4/40 pts, 2 of those are alive without signs of active LCH in other organs. There was no difference in response, survival, reactivations or pc between the Vinblastin and the VP-16 treatment arm.
In conclusion, the available data provide evidence that PI is a rare event in pediatric LCH, occurring usually in MS-disease. In particular, the combination of PI with liver involvement is associated with an unfavourable prognosis.

LONG TERM FOLLOW-UP OF PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH): RADIOLOGICAL FINDINGS IN THE LUNG CORRELATED TO SMOKING

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Patients with LCH were examined with chest X-ray and CT of the lungs, and the radiological findings were correlated to the patients smoking habits.
MATERIAL AND METHODS: A follow-up study of all LCH patients treated at the Dept of Pediatrics at Karolinska Hospital from 1963 to 1990 was performed. The follow-up time from onset of disease varied between 5 and 36 years (median 15 years).75/83 patients have been evaluated and 65/75 are still alive. 57/65 were radiologically examined, including chest X ray and lung CT.
RESULTS: 50/58 had no clinical or radiological sign of lung involvement at the time of diagnosis of LCH, but this was developed in 9 patients during follow-up. 4/9 were smokers and 2 of them had radiological findings consistent with histiocytosis of extensive degree, 1 patient had findings of lesser degree and the fourth a mixture of emphysema and histiocytosis. 5/9 were non-smokers and had various radiological findigs (3 histiocytosis of lesser degree, 1 multiple abcesses, 1 radiation-induced fibrosis after bone marrow transplantation).
9/57 had pulmonary involvement at the time of diagnosis of LCH. Radiological findings at follow-up were:
3/9 patients had no pathological findings, all were non-smokers and with a follow-up time of 12,15 and 16 years.
4/9 patients had thin walled cysts less than 10 mm in diameter typical for histiocytosis, 1 of lesser degree (follow-up 13 years) and 3 of extensive degree (follow-up 12, 19 and 31 years). The patient with mild degree was a non-smoker and those with extensive degree were smokers.
2/9 patients had emhysema, one of them had probably also cystic changes due to histiocytosis, both were smokers.
The radiological findings consistent with histiocytosis of lesser degree could only be seen on CT of the lung, whereas the other findings were seen on both chest X-ray and CT.
CONCLUSION: Radiological changes in the lungs in patients with LCH was found in 17/57 patients. The presence of radiological changes consistent with LCH and the severity appear to be correlated to the patients smoking habits. CT is superior to chest X-ray in histiocytosis of mild degree.

LIVER INVOLVEMENT IN MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS (MS-LCH). Results from the LCH-I Study.

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LCH-I was an international cooperative clinical trial for the tx of MS-LCH in which monotherapy with vinblastine (Vbl) and VP-16 was compared in a randomized manner. 125 patients (pts) were included in the study (64 Vbl, 61 VP-16). Liver involvement (LI) was found in 54/125 pts (43%) and was diagnosed at initial presentation in 46/54 pts (85%) or developed later in the disease course in 8 pts (15%). There were 31 male and 23 female, their age ranging from 1week to 4y 3m (med. 11m). Diagnosis of LI was based on clinical findings and/or pathological laboratory parameters. Hepatomegaly (liver size > 3cm below costal margin) was found in 47/54 pts. Abnormal values were documented in 34/54 pts. Total protein ranged from 28-54g/l (med. 45g/l), albumin from 15-25g/l (med. 22g/l). ALT from 50-399U/l (med. 87U/l), AST 58-379U/l (med. 134U/l). Other parameters were only sporadically documented. Liver biopsy was performed in 15/54 pts and showed abnormal histopathology in 13 pts. Liver fibrosis was reported in 5/54 pts with LI and was confirmed by biopsy in 3 pts. LI was most frequently associated with involvement of skin (89%), spleen (74%), hematopoiesis (67%), bone (67%), lymph nodes (61%), hematopoiesis (55%), spleen (50%), and lungs (44%). After 6 weeks of initial treatment (tx) a response was seen in 19/54 pts with LI, a disease progression occcured also in 19/54 (35%). An intermediate response was seen in 16 pts. 11/19 nonresponders (58%) died as opposed to 7/16 intermediate pts (44%) and 4/19 responders (21%). After a median observation time of 1y 3m (1m - 4y 9m) the probability of survival (pSU) was 76% for the whole study population. Overall 25/125 (20%) pts died. In pts without LI pSU was 95% versus 50% in pts with LI. 22/25 fatalities (88%) had LI, 18 of these 22 had abnormal liver function. In 18/22 pts (82%) with fatal outcome initial LI persisted until death, or developed during fatal disease progression in 4 pts. In 8/54 pts LI had resolved after initial tx at week 6, all these patients became finally free of disease according to the last available follow up evaluation. In concordance with the literature, mortality in the LCH-I study was highly associated with LI in particular with abnormal liver function. Nonresponse at week 6 and persistence of LI was associated with a high mortality. Conversely resolution of the disease in the liver after initial tx indicated a favourable outcome. This observation provides evidence that an early switch to salvage therapy in nonresponders with LI may be indicated.

LIVER TRANSPLANTATION FOR CIRRHOSIS COMPLICATING LANGERHANS' CELL HISTIOCYTOSIS

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Some children with Langerhans' cell histiocytosis (LCH) develop chronic liver disease. The pathogenesis seems to involve infiltration of large bile ducts by "LCH cells" leading to progressive biliary cirrhosis. For patients with "end-stage" disease, orthotopic liver transplantation (OLT) is an option. The aims of this study are a) report a case of multisystem LCH with end-stage liver disease treated by OLT and b) to review the published experience of OLT in LCH.

Case History: A one year old girl developed multisystem LCH and was treated with steroids and vinblastine, with initial response. At age 2.5 years she developed progressive end-stage liver disease due to sclerosing cholangitis and was transplanted with a right lobe liver graft. Post-transplant rejection episodes were treated with cyclosporin A (CyA), azanbioprine, steroids and subsequently FK506 for severe acute rejection. Six months post-transplant she developed and Epstein-Barr virus related lymphoproliferative disease (LPD). Immunosuppression was reduced and the LPD resolved. Eighteen months post-transplant she is currently well, though recent new "active" LCH (skin rash and bone lesions) necessitated a short course of steroid therapy.

Literature Review: OLT has been reported in 17 patients with LCH and end-stage liver disease. Pre-transplant data was available in 14 cases (7 male). Median age at diagnosis of LCH was 20 months (range 6- 36) and median age at transplantation was 78 months (range 24-204). Of 14 patients with sufficient data, 10 were in clinical remission from LCH prior to OLT. Vis-a-vis acute cellular rejection, data was available for 15 patients. 14 developed this complication and in 3 (21%) it was severe and intractable, necessitating re-transplant (1) or one case (sweet). Graft survival (n=21) is 71% and patient survival is 82% (median follow up 36 months, range 9-87). Of the 14 survivors, 8 were asymptomatic and 6 (35%) have need additional treatment for LCH post-OLT. There have been no instance of documented LCH recurrence in the transplanted liver. Other post-transplant complications include CMV infection, CNS toxicity due to CyA, Pneumocystes carinii pneumonia and GI bleeding.

We conclude that OLT is feasible and effective in LCH patients with end-stage liver disease. "Active" LCH in other systems is not a contraindication to this procedure.

A MORPHOLOGIC ANALYSIS OF LANGERHANS CELL LESIONS IN LYMPH NODES: A STUDY OF 43 SPECIMENS FROM 39 PATIENTS.

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The morphological features of Langerhans cell histiocytosis (LCH) in lymph nodes were analyzed in 43 biopsy specimens from 39 patients and the findings were correlated with clinical parameters. Five histological motifs were recognized: sinusoidal, limited sinusoidal, epithelioid granulomatous, partial effacement and total effacement patterns. Lesions were characteristically composed of histiocytes with the Langerhans cell (LC) phenotype, other histiocytes with the phenotype of macrophages, multinucleated giant histiocytes, T-lymphocytes and eosinophils in varying proportions. Proliferative activity was confined to S100+ lesional histiocytes in lymph nodes. PCNA proliferative indices ranged from 2.6 to 48% with largest indices being observed in specimens with total effacement and smallest in those with the epithelioid granulomatous pattern. Two of 25 evaluated specimens showed a hyperdiploid aneuploid DNA ploidy profile; both with the pattern of total effacement. Epithelioid granulomas composed of histiocytes with the LC phenotype dominated three abdominal specimens reflecting a picture of LCH not previously reported. These resembled the granulomas associated with Hodgkin's disease. The pattern of total effacement, seen in 3 patients, was associated with large numbers of unmarked histiocytoid cells, high proliferative indices, an aneuploid DNA ploidy profile in 2 specimens and, in 2, a fatal outcome. The third fatal case (total 3 among 39 patients) had a sinusoidal pattern but with extensive hemosiderosis that was judged to reflect strong activation of the mononuclear phagocytic system that is sometimes seen in cases of LCH. Different histologic patterns of LCH in lesions from separate sites in the same patient were seen in the 3 cases with epithelioid granulomatous LCH in lymph nodes and in 3 cases with total effacement of lymph node architecture. Extra-nodal lesions in these cases showed the characteristic histopathology of LCH. Conclusions: [1] The histopathological findings in lymph nodes involved by LCH are diverse and should be appreciated by those responsible for evaluation of such specimens. [2] The heterogeneity of lesions in different sites in the same patient suggests a strong influence by the local environment in which lesions occur. [3] Although the numbers of cases studied do not permit strong inferances, total effacement of lymph node may be an indicator of bad prognosis.

SECONDARY LANGERHANS' CELL HISTIOCYTOSIS (LCH) WITH PROMINENT MACROPHAGE DIFFERENTIATION: REPORT OF A CASE ASSOCIATED WITH MALIGNANT LYMPHOMA

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We report an unusual case of secondary LCH with prominent macrophage differentiation associated, in the same lymph node, with a high grade B-cell NHL. A 66 year-old man complained of night sweats, weight loss, moderate fever (37,5°C) and severe itching. Physical examination revealed many small reddish papules diffusely distributed, and varying impetiginized scratch lesions. Laboratory workup included: ESR (57mm/hr), CRP (7.1 mg/dl), leucocyte count (10,6x10^9/l), LDH (519 mU/ml), cupremia (235 µg/dl). Neither superficial lymphoadenomegaly nor hepatosplenomegaly was observed; histological examination of one skin lesion revealed a transient acantholytic dermatosis and a diagnosis of "Grover's disease" was made. Total body CT scan detected three enlarged deep-abdominal lymph nodes, whose histological examination prompted a diagnosis of high grade centroblastic B-cell lymphoma. The patient (stage IIB) underwent polychemotherapy (CHOP and VIP16 plus Vindesin), but he died of progressive disease 9 months after diagnosis. In one of the three lymph nodes, the sinuses were dilated by an heterogeneous population with elements predominantly resembling Langerhans' cells and interdigitating reticulum cells, multinucleated giant cells and few, scattered, large histiocyte-like cells reminescent of Rosai-Dorfman (RD) cells, exhibiting cytophagocytosis and showing a peculiar S-100+, CD1a-, CD68+, LN5-/+, Lysozyme -/+, cathepsin D+, cathepsin E+, LN3/HLA-DR- and CD30+/-, antigenic profile. In addition, lymphocytes, plasma cells and eosinophils, were admixed.
Several reports have documented an association of LCH and Rosai-Dorfman disease (RDD) with malignant neoplasms. In our case the cellular infiltrate showed ambiguous cytomorphological and antigenic (S-100+;CD1a-;HLA-DR; CD68+) features, borderline between LCH and RDD. Cases similar to ours have been reported in the registry of RDD (case n°369) and in the series of LCH described by Ruco (case n°3). The former was interpreted as due to the coexistence of LCH and RDD in the same lymph node, whereas the latter was considered a rare form of LCH with macrophage differentiation. Cytokines affect the distribution and differentiation of dendritic cells/Langerhans' cells in primary lung carcinoma. We believe a similar mechanism may operate in our case, where the lymphoma cells could alter cytokine release, leading to the histopatologic and antigenic peculiarities of the LCH-like proliferation. Even our findings in this non-neoplastic case support the hypothesis of a possible relation between LCH and RDD.

NON-LANGERHANS CELL HISTIOCYTOSES - A NEW UNIFYING CONCEPT.

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Based on a series of 153 cases of non-Langerhans cell histiocytoses we present a new unifying concept on this rare group of disorders. The common denominator is the monocyte/macrophage, which presents with various histologic features probably due to the influence of cytokines. Non-Langerhans cell histiocytoses are classified according to the predominant mononuclear (vacuolated, spindle-shaped, xanthomatized, scalloped, oncocytic) and/or multinucleate (Touton, ground glass appearance, Langhans, foreign body) histiocytic cell type. Variable mixtures of these cell types produce common polymorphous patterns with prominence of vacuolated, spindle-shaped and xanthomatized histiocytes in juvenile, of scalloped and oncocytic in adult xanthogranulomas. Rarely, unusual monomorphous reaction patterns, mostly vacuolated histiocytes, are observed in the mononuclear variant of xanthogranulomas, (early) benign cephalic histiocytosis and generalized eruptive histiocytoma. Xanthomatized histiocytes predominate papular xanthoma and rarely xanthoma disseminatum, whereas spindle-shaped histiocytes are evident

in spindle cell xanthogranuloma and progressive nodular histiocytosis, and scalloped histiocytes in most cases of xanthoma dissemination, finally oncocytic histiocytes in reticulohistiocytoma and multicentric histiocytosis. Immunohistochemical, ultrastructural and clinical findings can rationally be adjusted to this unifying concept of non-Langerhans cell histiocytoses. The time course of lesions, the age of the patients and the presence or not of underlying internal diseases are, or may, at least partially, be related to and thus explain variations on the theme of the non-Langerhans cell histiocytic reaction.

DIFFERENTIAL EXPRESSION OF CELL GROWTH MEDIATORS IN MALIGNANT HISTIOCYTOSIS.

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Recent studies have described cell differentiation in Malignant Histiocytosis (MH) along the monocyte/macrophage lineage. It is well established that activated macrophages are capable of producing a number of cell growth mediators and cytokines. Therefore we determined the type and quantity of a serie of growth factors produced by MH DEL cells t(5;6)(q35;p21) in comparison with other histiocytic lymphoma derived cell lines including SU-DHL-1 t(2;5)(p23;q35) and U-937, promyelocytic cells HL-60 and with cellular material from infiltrated lymph node from a patient with MH carrying t(2;5)(p23;q35) chromosome abnormality.

Using both reverse transcription-polymerase chain reaction (RT-PCR) and Northern blot analysis, high level of TGF-α, TGF-β, PDGF-A and EGF mRNA were detected in DEL cells as well as in the MH lymph node material. Conversely, lower levels of TGF-α, TGF-β and EGF were detectable in SU-DHL-1 and U-937 cells. In HL-60 cell line, only TGF-β specific transcripts were detected. Comparative analysis between TGFα, TGFβ, EGF and PDGF-A immunolabeling and their expression at mRNA level in the various cell lines and the MH tissue sample is in progress. The table shows semi-quantitative data from the Northern blot analysis:

Cell type	TGF-α	TGFβ	EGF	PDGF-A
DEL	+++	+++	+++	+
MH tissue	++	ND	+++	ND
SU-DHL-1	+	ND	++	ND
U937	+	+	-	ND
HL-60	-	+	-	ND

Since TGF-α, an epidermal growth-related factor, is not usually expressed in cell lines of hematopoietic origin or in human mature cells, its expression in histiocyte-related cells is probably of significance and should be relevant to the unexpected expression of the Epithelial Membrane Antigen in CD30+ MH. Remarkably, TGF-α expression in histiocyte-derived cell lines provides an additional differential element in the discussion on the lymphoid or histiocytic nature of these lineages.

MUTATIONS OF THE TUMOR NECROSIS FACTOR-ALPHA GENE (TNF-α) PROMOTER IN LANGERHANS CELL HISTIOCYTOSIS (LCH) PATIENTS AFFECT GENE TRANSCRIPTION

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Introduction: To better understand the pathophysiology of TNF-α upregulation in LCH we have surveyed the DNA sequences controlling transcription of that gene in LCH patients. **Materials and Methods:** DNA from the lesions of twelve LCH patients and four normal individuals were screened from mutations in the TNF-α promoter (600 bases 5' of the transcription start site). Initial screening of 200 base segments was done by the Single Strand Conformational Polymorphism (SSCP) and then by DNA sequencing to confirm any abnormalities suggested by SSCP. Functional consequences of the mutations were defined by cloning the normal and mutated TNF-α promoter sequences into a promoter-less luciferase plasmid pGL-3 (Promega) and measuring the quantity of light emitted by the luciferase substrate in a liquid scintillation counter. Nuclear factor binding to the mutated promoters as compared to normal sequences was determined by a gel-shift assay. **Results:** 5/12 LCH patients had mutations in the TNF-α promoter. Two patients with multiple bone lesions had a G→A transition at nucleotide -308 (a known polymorphism). One of these also had a T→C transition at -309. One patient with multisystem disease had four mutations in other regions. Two patients with unifocal bone disease had single base mutations. The luciferase assay showed a 3.5 to 7-fold increased promoter activity for those with the -308 polymorphism, but not the other mutations. Likewise the gel-shift assay illustrated markedly different nuclear factor binding to the promoters with the -308 polymorphism. **Conclusions:** Some mutations in the promoter of TNF-α can upregulate gene expression and allow increased production of this cytokine in LCH patients. A polymorphism at position -308 may prevent binding of a repressor protein accounting for this effect.

Lack of expression of E-cadherin is associated with dissemination of Langerhans cell histiocytosis and poor outcome

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Langerhans cell histiocytosis (LCH) often occurs in children as a cutaneous disease. The course of the disease is characterised by spontaneous resolution or multivisceral dissemination of poor prognosis. The pathogenesis of LCH is not known. Since E-cadherin mediates homophilic adhesion of normal Langerhans cells to keratinocytes and is also a ligand for the αEβ7 intraepithelial lymphocyte integrin, we investigated whether its expression on LCH cells correlates with the clinical behaviour of the disease.

We retrospectively analysed clinical records of 14 children with LCH, all of which had cutaneous involvement. The expression of E-cadherin was studied by in situ immunohistochemistry on 22 frozen biopsy samples with two specific monoclonal antibodies.

LCH cells of the 7 children with only skin involvement were positive with E-cadherin. By contrast, LCH cells of the 7 children who further developed extensive LCH disclosed a negative or low expression of E-cadherin.

Our study shows that dissemination and poor prognosis are associated with lack of E-cadherin expression on LCH cells. Aggressive clinical evolution of LCH may therefore be related to the loss of functions mediated by E-cadherin.

EPIDEMIOLOGICAL STUDY II ON CHILDHOOD LANGERHANS CELL HISTIOCYTOSIS (LCH) IN JAPAN.

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The first epidemiological study for childhood LCH in Japan was performed during 1986- 1990 and the results were published in JJPHO(1:241-246,1994) We conducted the second national survey for the newly diagnosed LCH cases between 1991 and 1995 and the data were compared for these two studies *Methods* . Questionnaires designed to collect information on family history ,past history, clinical features, therapy and prognosis were sent to 939 members of the Japanese Society of Pediatric Hematology . In the current study , we particularly attemted to obtain detailed information on the family and past history in understanding the etiology and pathogenesis of LCH. Also response/relapse patters were analyzed to establish a refined therapeutical protocol *Results* Of the total 126 cases, the median age was 2 9(68.2% were less than 3) and 70 females. Family history revealed malignancy in 9.5 % and past history showed that about 60 % were immunized with polio myelitis and tuberculosis. 42% for DPT and only 3.1% for varicella.. Growth retardation was seen in 7 cases. Clinical features were similar to those in the previous study: palpable tumors(34.9%),fever(28.5%), skin rash (26.9%), bone pain(22.2%) and hepatosplenomegaly(21.4%) Bone was the most frequently involved site(68.2%), in order of skull> femur> spine> pelvis Response(CR+PR) to initial treatment was obtained in 92 cases(73%), NR in 4 cases, with 14 cases still in induction BMT was successfully performed in 2 cases. Relapse occured in 30.9%, with one relapse in 26 cases, two in 8 cases, and 3 in 5 cases. Twelve cases died of multiple organ involvement except for 2 cases and they were all less than 3 years old Among them ,6 cases suffered from pulmonary involvement Mortality,9.5%, was compatible with that(7.8%) in previous survey *Conclusion* Impact of immunization and other past history on LCH development in these cases is under analysis Considering high rate of relapse, although initial response was good, new treatment strategies are required in future for pediatric patients with LCH

LONG TERM FOLLOW-UP OF 83 PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH) - A SINGLE CENTER STUDY

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This study was performed to elucidate the long term effects of LCH and its therapy.
MATERIALS AND METHODS: A follow-up study of all LCH patients treated at the Dept of Pediatrics, Karolinska Hospital, Stockholm, 1963-90 was performed. Of 83 patients, 75 were children aged 0-15 yrs at onset (median 2 yrs 6 mo) (44M/31F) and 8 were adults aged 16-42 yrs at onset (median 26 yrs) (5M/3F). 73/83 patients are alive. During the period febr-95 to febr -96 the medical records of all the patients were reviewed. In addition, a physical examination of 65 patients was performed by the same physician and these patients also completed a questionnaire. The follow-up time from onset of disease varied between 5-36 yrs (median 15 yrs).
RESULTS: Of the children 5 had multisystem disease (MS) with organ dysfunction at onset, 20 had MS. 11 multifocal bone disease (MF). 29 a solitary bone lesion, 7 localized skin disease. 2 diabetes insipidus (DI) and one had lymph node enlargement as the only sign of disease at onset. 69/75 pts were treated with either surgery, irradiation, steroids and/or chemotherapy. One of these pts was treated with BMT after 10 yrs of recrudescences. 6 pts had only "a wait and see" regimen. 66/75 pts are alive. 58/66 have been examined. 31 have at least one long term side effect of their disease and/or the therapy. 10 pts have DI, 9 receive other hormonal replacement, 9 have short stature, 7 orthopedic problems, 11 facial asymmetry, 6 abnormal dentition, 6 CNS abnormalities and 3 pts have been treated for a secondary malignancy. Of the 8 adults 5 had MS with pulmonary dysfunction at onset, one had MS at onset and developed pulmonary dysfunction and 2 had MF. One of the adults died (in pulmonary hypertension).
CONCLUSION: Although mortality in LCH in children is low (7/75 (9%) in our study), the number of examined survivors with permanent sequelae is significant (31/58 (53%)). Of the adult pts the majority have pulmonary dysfunction. Improved therapy aiming at reducing mortality and morbidity is desireable.

A 20 YEARS RETROSPECTIVE ANALYSIS OF THE SWISS MULTICENTER LANGERHANS CELL HISTIOCYTOSIS STUDY 76.

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From 1976-1986 45 children (23 boys, 22 girls), medium age 5,5 years) with Langerhans cell histiocytosis (LCH) were treated with the prospective SPOG-HX76 treatment study, stratified according to well known risk criterias (bone, soft tissue and organ involvement). Unisystemic, single site disease of the bone was treated with surgery and/or radiotherapy without systemic therapy. For multifocal skeletal disease a 2 year 6MP maintenance therapy was given after 6-8 weeks Vbl/Pred induction chemotherapy.
Extraosseous LCH (skin, lymph node, GI, liver, lung, CNS and BM) was treated with risk adapted Vbl/Pred pulses in addition to the above mentioned chemotherapy. Patients with malignant LCH were treated with COAP and patients with relapse again with Vbl/Pred/ 6MP-, no VP16 was given.
Single system bone disease with either uni- or multifocal lesions were observed in 10 (22%) and 21 (46%) children. Extraosseous- and organ LCH occurred in 19 (42%) and 10 (22%) of all 45 patients.
As of January 1996, 36 (80%) children could be contacted with a questionnaire. 9 children were lost for follow up due to emigration, but nevertheless they could be seen in the centers for a minimum of 3 to 9 years (medium 5,5) post diagnosis.
The overall survival of the whole patient cohort is 93%. 3 children died, 1 with CT resistant lung LCH, 1 with intracranial pressure and herniation due to a cerebellar malignant LCH- mass and 1 with end stage liver LCH.
The 11 children (24%), who relapsed could successfully be retreated and are now without active disease. 10 children (22%) have late sequelae with a predominance of endocrine dysfunction (Diabetes insipidus 5, GH deficiency 2, hypothyreosis 2).
2 children are mentally retarded, 2 have sensory deficits (amaurosis 1, hearing loss 1) and 3 show orthopedic disabilities. With the exception of 2 children all express normal schoolprofessional- and social integrity.

RISK OF SECONDARY LEUKEMIA (s-ANLL) AFTER LANGERHANS' CELL HISTIOCYTOSIS: ANALYSIS OF THE ITALIAN AND AUSTRIAN-GERMAN-DUTCH-SWISS COHORTS

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To evaluate the risk of s-ANLL after treatment for LCH we studied all subjects treated according to cooperative protocols in Italy or in Austria, Germany, Holland and Switzerland (AGDS). For each subject, information was collected on the cumulative dosages of chemotherapy and radiotherapy received, vital status and occurrence of secondary leukemia. The expected number of leukemias were estimated using age-specific incidence rates of the two most established cancer registries in Italy and Germany. Standard incidence ratios (SIR) were used to measure the risk of secondary

leukemia among LCH patients. Stratification was done according to the exposure to VP-16 and to the cumulative dose of VP-16. The Italian cohort contributed 241 subjects for a total of 1535 person-years-risk (PYR); the AGDS cohort consisted in 363 patients; they contributed for 1981 PYR. Five leukemias occurred within the Italian cohort (SIR 520; 95% C.I. 168 - 1213), whereas no cases have been reported among the AGDS patients. Although the 5 patients had previously received a dose of VP-16 ≥4,000 mg/m², the s-ANLL were all FAB M3 and lacked most of the characteristics described for epipodophyllotoxins-related leukemias. The number of s-ANLL among the Italian subjects exposed to VP-16 was more than 1,000 times greater than expected based on the general population rates. Among the AGDS cohort very few subjects were exposed to high doses of VP-16. High doses of VP-16 appear to increase the risk of s-ANLL in LCH patients. These findings, and the evidence of a higher incidence of M3 among Italian and Latino populations, suggests that high doses of etoposide in subjects of Latino origin may increase the risk of aberrations on chromosomes 15 and 17.

LANGERHANS CELL HISTIOCYTOSIS (LCH): A STUDY OF EFFECTS ON LEARNING OUTCOMES AND PSYCHOSOCIAL ADJUSTMENT

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Anecdotal and clinical reports link LCH to changes in central nervous system (CNS) functioning among some diagnosed children. The precise incidence is unknown. A sparse empirical data base show that CNS based symptoms may lead to various chronic difficulties in neurological, neuropsychological, and academic functioning. The study's aims were (1) to identify early and late elementary school reading and mathematics achievement levels of children diagnosed with LCH (2) to assess the pattern of elementary school achievement (3) to determine the frequency of psychosocial adjustment problems. Twenty-two children diagnosed with LCH before 5 years of age and currently between 11 and 16 years of age and their parents participated. Statistical analysis of early and late achievement test scores revealed no significant difference between the sample and the normal population. The achievement levels were remarkably consistent across elementary school. Compared to the norm group, 18% experienced problems with competence (school only) and 23% demonstrated clinically significant behavioral problems (primarily internalizing). The small sample size constrains generalizing to the LCH population. Controlled retrospective and prospective studies of neuropsychological and psychosocial aspects of children with LCH are needed to confirm these pilot study observations. We conclude: (1) Most survivors of LCH appear similar to the normal population in reading and mathematics achievement, as well as, psychosocial adjustment. (2) When survivors of LCH do show below average reading and mathematics achievement, these difficulties emerge early and persist. (3) Adolescent survivors of LCH are at a slightly higher risk than the normal population for clinically significant behavior problems.

INDOMETHACIN - A USEFUL "ADJUNCTIVE" THERAPY IN LANGERHANS CELL HISTIOCYTOSIS (LCH) - EXPERIENCE AT GREAT ORMOND STREET, LONDON 1984-95.

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Patients with LCH often suffer discomfort or pain, especially from bone lesions. Because prostaglandins (PG)E2 and F have been identified in LCH lesions we have used indomethacin (IND), a known PG inhibitor, in those patients symptomatic from bony LCH in whom we wanted to avoid steroids or chemotherapy, or in whom these treatments did not provide complete symptom relief. The purpose of this study was to review our experience on the use of IND in LCH. We have treated 10 patients with bony disease between 1984 - 1995; 6 with single system disease and 4 with multi-system disease. Age ranged from 2 - 15 (average age 6.8 years) at the time of IND therapy and there were 7 boys and 3 girls treated. All patients treated with IND had bone disease - 9 of these complained of pain and one was treated because of discharging scalp lesions. 9 patients received IND as sole therapy and 1 patient received a combination of low dose prednisolone and IND. 6 patients had received no previous therapy, 2 had received intra-lesional and oral steroids , 1 patient had received prednisolone, vinblastine and thymosin, and 1 patient prednisolone and 6 mercaptopurine prior to treatment with IND. The dose of IND ranged from 9 - 200mg/day in divided doses (1 -2.5mg/kg/day) and was given for 1 - 16 weeks (average 6 weeks). Results: 8 patients had a complete response to treatment (defined as complete disappearance of symptoms for 4 weeks). 3 patients had one course of IND and have remained symptom free. 4 patients have had repeated courses of treatment with good symptom control and one patient remains on continuous IND at a dose of 1.5mg/kg/day (10 mg tds). One patient with suppurative scalp lesions failed to respond to indomethacin therapy. IND was well tolerated except for possible drowsiness in 1 patient and with no gastrointestinal side effects although one patient was withdrawn from therapy because of concern over potential interaction between anti-convulsants and IND .We conclude that indomethacin is a useful adjunctive therapy in both multi-system and single system LCH and may spare some children radiotherapy, steroids or chemotherapy which are either more invasive, or have unwanted side-effects. There is a case for a formal study of indomethacin as first-line treatment in symptomatic single system bony disease.

GRANULAR LYMPHOCYTE PROLIFERATIVE DISORDERS (GLPD) ASSOCIATED WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN EARLY CHILDHOOD. Characteristic bone marrow morphology and hypercytokinemia

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HLH consists of primary and secondary disorders. Primary disorders are familial and secondary disorders are associated with various infections or lymphomas. Previously, secondary HLH has been reported in connection with GLPD with or without Epstein-Barr virus (EBV) infection in adults; however, no similar correlation has been reported for young children.

We report 5 pediatric cases of HLH which showed proliferation of characteristic granular atypical lymphocytoid cells in bone marrow. All cases were girls aged 8 months to 4 years who had marked hepatosplenomegaly. Marker analysis on peripheral blood mononuclear cells revealed an increase in the CD3+HLADR+ subset in 3 cases and the CD3+CD56+ subset in 1 case. An EBV genome was detected in 3 cases, and monoclonality was confirmed in 2 cases. A characteristic morphology of large granular lymphocytes (LGL) was identified in our cases, with elongated bizarre-appearing features that resembled horsetail-, tadpole-, cucumber-, or shooting star-type configurations on the bone marrow smear. In these cases, LGLs in the peripheral blood smears escaped notices at the laboratory and the diagnosis was only made possible by bone marrow aspirations. Serum concentrations of soluble interleukin-2 receptor and interferon-gamma were markedly elevated in all cases. All 5 cases required multi-agent chemotherapy, with 2 complete remissions, 2 partial remissions and 1 no response. Refinement of treatment is required for these pediatric cases which probably comprise specific high risk subgroup among heterogeneous secondary HLH patients. Caution must be exercised to keep GLPD-associated HLH in mind in the differential diagnosis of secondary HLH even for young children.

INTERFERON-γ (IFN-γ) AND INTERLEUKIN 10 DOUBLE-POSITIVE T CELLS AS POTENT ACTIVATORS OF AN UNCONTROLLED HYPERINFLAMMATORY RESPONSE IN PATIENTS WITH FAMILIAL- AND INFECTION- ASSOCIATED HISTIOCYTOSIS

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In 18 patients with either infection-associated histiocytosis or familial histio-cytosis (FHL) cytokine profiles and cellular cytotoxicity were tested in an active phase of the disease, and before treatment. Remarkably, 14 patients were unique by the simultaneous presence of the inflammatory cytokine IFN-γ (100 - 1500 pg/ml) and the anti-inflammatory cytokine IL-10 (50 to 4000 pg/ml). Concomitantly, the plasma concentrations of TNF-α showed elevated levels rangeing between 60-800 pg/ml. In addition, the macrophage inflammatory protein-1α (MIP-1α) which downregulates proliferation of hematopoietic cells and stimulates macrophage functions was increased and higher than 70 pg/ml in all cases. T cell activation was difficult to document by flow cytometry since the high affinity IL-2 Receptor-positive (CD25+) T cells almost never exceeded 5 - 10% of total lymphopcyte population. In contrast, high levels of soluble CD25 were measured by a chemiluminescent immunometric assay in the plasma (about $5x10^3$ U/ml, with $5x10^4$ U/ml as the highest levels). This indicates that these hyperactivated T cells rather reside in the tissues than circulate. According to the recently established regulatory scheme on cytokine interactions (see Trinchieri and Gerosa 1996 for a review), the IFN-γ/IL-10 double positive T cells are induced by interleukin 12 (IL-12) from accessory cells and represent the strongest evidence for excessive proinflammatory cytokine responses with the consequence of serious tissue toxicity. The evidence for the involvement of IL-12 solely for the induction but not for the maintenance this TH1/TH2-type inflammatory cell type is further substantiated by high amounts of CD80 and/or CD86 positive cells in the lymphocyte population as well as the monocyte population of the patients' cells. We propose the unlimited activation of this distinct T cell population to represent a primary event in the manifestation of active histiocytosis.

*G. Trinchieri, F. Gerosa: Immunoregulation by interleukin-12. J. Leukoc. Biol. 59: 505-511 (1996).

HIGH FREQUENCY OF TUMOR NECROSIS FACTOR-ALPHA (TNFα) GENE PROMOTER MUTATIONS IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Patients with HLH present with fever, hepatosplenomegaly, lymphadenopathy, and coagulopathy. Markedly elevated levels of TNFα and interferon gamma have been documented in the serum of these patients. No mechanism has been proposed for these findings other than possible infectious agents triggering excessive production of otherwise normal inflammatory cytokines. We postulated that elevated levels of TNFα could result from abnormalities in the DNA sequence controlling expression of that gene. **Materials and Methods:** The TNFα promoter region was assayed for mutations in 24 patients with HLH by alterations in the Single Strand Conformational Polymorphisms (SSCP) of the 600 base pairs (bp) 5' of the transcription start site (TSS) for TNFα. Three fragments of 200 bp each were amplified, denatured and separated by electrophoresis through a MDE gel. DNA bands were identified by silver staining and compared to controls. **Results:** Of the 24 HLH patients, 19 demonstrated shifts of one or more bands indicating mutations or polymorphisms of the TNFα promoter. Four patients had more than one mutation demonstrated by SSCP. Fourteen had mutations/polymorphisms in the first 200 bp "upstream" (bp 0 to -200) of the TSS. Four had mutations/polymorphisms in bp -200 to -400, and 5 had mutations in the -400 to -600 region. **Conclusions:** Mutations in the TNFα promoter occur with unusual frequency in patients with HLH and could possibly be the cause of increased TNFα production in these patients. The specific location of these mutations/polymorphisms is being defined by DNA sequencing. Functional significance of these mutations/polymorphisms is yet to be determined.

FAS IS EXCLUDED AS A MAJOR GENE FOR HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Several lines of evidence implicate perturbance in T-cell regulation of macrophage activation in the pathogenesis of HLH. The Fas (CD95) transmembrane glycoprotein receptor is expressed by activated lymphocytes. Binding of Fas to its cognate ligand triggers apoptosis and plays a crucial role in lymphocyte homeostasis. Inherited Fas deficiency has been shown to be associated with lymphoproliferation accompanied in some cases by haemophagocytosis. We therefore sought to determine whether Fas defects contribute to the genetic basis of primary HLH. Fifteen patients (10 male, 5 female) aged 6 days to 2.5 years were studied. These included 3 familial cases defined on the basis of a previously affected sibling (1) or parental consanguinity (2). The entire 2.5 kb Fas coding sequence and splice sites flanking all 9 exons were screened for mutations by PCR-SSCP analysis. Other than known coding sequence polymorphisms no SSCP band shifts, when compared with controls, were detected among patient samples. We conclude that Fas deficiency is unlikely to be a major genetic determinant of HLH. During the course of the study we identified a novel C/G polymorphism within intron 5 of the Fas gene. Population studies revealed this marker to be more informative than previously reported polymorphisms. This will facilitate further investigation of the relation between Fas deficiency and human disease.

Treatment of Familial Hemophagocytic Lymphohystiocytosis with Bone Marrow Transplantation from HLA Mismatched Related Donors.

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Familial Hemophagocytic Lymphohystiocytosis (FHL) is a rare genetic disorder associated with the early onset in life of overwhelming activation of T lymphocytes and macrophages invariably leading to death. Allogeneic Bone Marrow Transplantation (BMT) from an HLA identical related donor is the treatment of choice in patients with this disease. However, less than 20 % of patients have a disease free HLA identical sibling. BMT from HLA-non-identical related donors has previously met with poor results with graft rejection being a major obstacle in all cases. We describe herein BMT from HLA non-identical related donors performed in 2 centers in 11 ascertained cases of FHL. Complete remission of disease was achieved before BMT in all patients. Marrow was T cell-depleted to minimize GVHD. In order to help prevent graft rejection, anti-adhesion antibodies specific for the α chain of the Leukocyte Function Associated Antigen 1 (CD11a) and the CD2 molecules were infused pre-and post bone marrow transplantation in addition to a conditioning regimen comprising busulfan, cyclophosphamide and etoposide. Sustained

engraftment was obtained in 8 transplants and disease-free survival in 6 patients with a follow up period ranging from 6 months to 64 months (mean 36). No GVHD was observed. Toxicity due to the BMT procedure was low. The results obtained by the use of this protocol are promising in terms of engraftment and event free survival within the limitation of the small sample. We conclude that BMT from HLA non-identical related donors using conditioning regimen including anti-adhesion molecules is an alternative treatment that warrants further study in FHL patients who lack a suitable HLA-identical donor.

CENTRAL NERVOUS SYSTEM (CNS) COMPLICATIONS OF INFANTILE HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): NEURORADIOLOGIC FINDINGS PRE AND POST BONE MARROW TRANSPLANTATION (BMT)

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Introduction: CNS involvement with infiltrating activated mononuclear cells is found in a majority of young children at diagnosis of HLH, 14/20 in our experience. The purpose of this analysis was to evaluate the usefulness of neuroradiologic imaging in diagnosis and follow-up of CNS disease in children receiving systemic chemotherapy, intrathecal chemotherapy and bone marrow transplantation for management of HLH.
Materials and Methods: Eighteen children with HLH underwent magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis, prior to and following treatment.
Summary of Findings: Symptomatic presentation of CNS disease included, in descending order of frequency, irritability and abnormal muscle tone, seizures (including 2 patients who developed infantile spasms), loss of developmental milestones and blindness. Prior to treatment, white matter T2 signal hyperintensity was the most common abnormal finding. In patients less than one year of age CNS involvement with HLH was more accurately assessed by CSF abnormalities (increased protein , mononuclear pleocytosis) than by MRI. Following treatment of the CNS, principally with intrathecal methotrexate , marked volume loss was frequently observed accompanied, in some patients, by extra axial fluid collections. Additional changes felt to reflect necrotizing leukoencephalopathy such as infarction and calcifications were observed in patients who had received the most extensive pretransplant treatment. Healthy longterm survivors of BMT have experienced reversal of cerebral atrophy and have compensated significantly for previous developmental delays
Conclusions: CNS involvement with HLH at diagnosis does not preclude successful BMT As more infants are apparently being cured of HLH by BMT, longterm follow-up of CNS disease, its structural sequelae and functional/developmental consequences will become important measures of overall therapeutic outcome.

LIVER AND PULMONARY INVOLVEMENT IN MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS (MS-LCH). Results from the DAL HX-83 and 90 studies (DAL).

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The aim of this retrospective analysis was to explore the clinical importance of liver (LI) and pulmonary (PI) involvement in patients (pts) with MS-LCH. 63 MS-pts (M:F=33:30, median age 11mo) were included in the DAL studies. LI was found in 32/63 pts (51%) At inital presentation LI was seen in 30/32 pts (94%). 2/32 pts (6%) developed LI during their course PI was diagnosed in 17 pts (27%), in 15/17 pts (88%) at diagnosis and in 2 pts (12%) during follow up evaluation Combination of LI and PI occured in 12/63 pts (19%). Diagnosis of LI was based on clinical and/or abnormal laboratory findings in all 32 pts, additionally supported by abnormal histopathology in 6 of them. Hepatomegaly was documented in 29 pts. Abnormal liver tests were documented in 17/32 pts. Total protein ranged between 28-50g/l (median 42g/l), albumin between15-23g/l (median 20g/l) Increased bilirubin up to 10mg/dl was observed in 3 pts and abnormal transaminases(ALT 79 U/l, AST 55 U/L) in only 1 pt. Other parameters were not sufficiently documented LI was most frequently associated with involvement of skin (81%), spleen (75%), hematopoiesis (72%), lymph nodes (69%) and bone (59%). PI was diagnosed radiologically in all pts. Histological confirmation of PI was obtained by open biopsy in 2 pts. Pulmonary function tests and BAL were either not performed or not available for the analysis. PI was most often combined with involvement of skin (94%), liver (71%), hematopoiesis (59%), spleen (59%) and lymph nodes (53%). The probability of survival (pSU) was 100 % in the 26 pts without LI or PI. LI showed a pSU of 75%(12/32 pts with LI died). None of the 5 pts with PI without LI died. In pts with a combination of LI and PI the pSU was only 42% (7/12 pts died) LI had completely resolved in 13/20 survivors and improved in another 7/20 survivors after 6 weeks of initial therapy Conversely, in 11/12 pts with fatal outcome initial LI persisted without improvement until death, or developed during fatal disease progression in 1/12. 11 of the fatalities with LI had abnormal liver function Two of those 11 had liver fibrosis and signs of sclerosing cholangitis. Lung fibrosis developed in 1 pt In accordance with the literature, LI and especially the combination of LI with PI carry an unfavourable prognosis. They were associated with high mortality in the DAL, although risk-adapted intensive polychemotherapy was applied. Our data further support the observation that nonresponse to initial treatment in critical organs is associated with a high risk of mortality and therefore the application of aggressive and experimental salvage treatment modalities is justified.

Digestive tract involvement in Langerhans cell histiocytosis.

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Background. Langerhans cell histiocytosis (LCH) is a rare disease with a wide clinical spectrum. Although little is known of gastrointestinal involvement in LCH, it may be a major clinical problem. We investigated clinical, pathological and immunohistochemical features of children with digestive tract LCH involvement.

Patients. Selection criteria: LCH with digestive symptoms and histological confirmation of gastrointestinal involvement. Seven children (2%) met the criteria among 348 cases of LCH in a national retrospective survey of 1983-1993 in France. Two children diagnosed in 1994 were also selected. As controls for immunohistochemical experiments, frozen biopsies from 7 patients with LCH without digestive symptoms were also studied.

Results. Patients: 9 children with LCH and digestive tract involvement were studied. Clinical features at presentation: skin (9/9) and mucosal (4/9) involvement. Failure to thrive (5/9), diarrhea (7/9), bloody stools (4/7), vomiting (4/9), and hypoalbuminemia (8/9). Mortality: 5/9. Factors of poor prognosis: young age, organ dysfunction (stage 4) and need for parenteral nutrition. Unlike control biopsy specimens, LCH cells of children with digestive tract involvement disclosed expression of the mucosal homing receptor integrin $\alpha 4\beta 7$ on frozen skin and digestive tract biopsy specimens.

Conclusion. Digestive tract involvement in LCH is a clinico-pathological entity, occurring in children with cutaneous or/and mucosal LCH. As prognosis and treatment of LCH depend on the extent of the disease, treatments of these disseminated forms should not be delayed, thus children with cutaneous LCH and digestive symptoms should undergo digestive tract biopsies. Studies of homing receptors may contribute to understanding the mechanisms of dissemination in LCH.

VISCERAL SEQUELAE IN LCH

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The aim of this report is to present the features of lung and liver sequelae in LCH, in the 137 patients (pts) followed in our hospital from mar.87 to march 96, with a mean follow up of 53 months (mo). Nineteen pts(14%)had lung involvement (inv)and 6 of them(4.4%)had a chronic interstitial and bullous compromise. The median age was 50.5 mo(r: 23 to 152), and 3 pts were male. Other inv in this pts included : bone (5),ENT (5),diabetes insipidus (2), skin (1) and liver (1). No other organ dysfunction was detected. They were treated by chemotherapy (C)(prednisone(pr)-vinblastine(VB): 2 pts, pr-vincristine: 1, DALHX 83: 1, LCH-I(VP16): 1, LCH-II(VB): 1, 5/6 pts remain with a stable chronic pulmonary inv with no other evidence of active disease (median follow up: 79 mo, R: 37 to 98). One pt died with progressive LCH disease and secondary myelofibrosis. Twenty one pts(15%)had a liver inv but 6 of them (4.4%)had a chronic liver sequelae. The median age was 27 mo(r:19 to 36 mo) and 3 pts were female. Other inv in this pts were: bone:3, ENT:2, CI:2, skin:1, lung:1, lymph nodes: 1, spleen:1. Ultrasound showed periportal hypoechoic areas. Liver biopsy was done in all cases: sclerosing cholangitis and/or cirrhosis were found, wich was confirmed by cholangiography in 4 pts. All childrens were treated by C (LCH I-VP16: 4 pts, LCH I-VB:1, pr-VB:1). The median follow up was 26 mo (r:13 to 38) and 4/6 pts survive with chronic liver sequelae: 2 with stable disease and 2 with chronic progressive inv(one were transplanted and survive 1 mo thereafter and the other pt is scheduled for liver transplant in the near future). Two pts died of encephalitis and progressive hepatic dysfunction with sepsis. We conclude that liver and lung sequelae were usually detected in pts over 2 year old, with stable pulmonary and progressive liver damage, with no response to the C. Liver transplant may be the treatment choice in cases with progressive liver compromise.

SPINE INVOLVEMENT IN LANGERHANS CELL HISTIOCYTOSIS (LCH)

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Bone lesions are the most frequent manifestation in LCH and can mimic a variety of other diseases. In particular, in vertebral lesions malignancies like e.g. Ewing sarcoma must be considered in the differential diagnosis. Involvement of the spine can compromise spinal stability with secondary neurologic impairment and, therefore, presents both a diagnostic and therapeutic challange. From 275 patients (pts) under the age of 18 with newly diagnosed LCH registered in the multicentric DAL-HX 83 and DAL-HX 90 studies, 253 (92%) pts were diagnosed as having bone involvement. In this retrospective study we focused on the 41 pts (16%) with spine involvement. We describe early symptoms, site of lesions, diagnostic procedures, treatment, clinical course and permanent consequences (pc). 17/41 pts (41%) presented with unifocal bone involvement (UFB), 14 pts (34%) with multifocal bone involvement (MFB) and 10 pts (25%) with multi system LCH (MS). The mean age at diagnosis was 7y10m (range 3m-17y 1m). Early symptoms (pain, swelling, neurological signs) due to spine involvement were present in 29 pts (71%) at a median onset of 3m (range 1week - 14m) before diagnosis. In the 41pts a total of 73 vertebral lesions was found. The vertebral body was most frequently involved (45 lesions = 62%). Six lesions (8%) were detected in the vertebral arch, 8 (11%) involving both, vertebral arch and body. In 14 lesions (19%) the exact localisation could not be determined. The thoracic (46 lesions = 63%), lumbar (17 lesions = 23%) and cervical spines (10 lesions = 14%) were involved in descending order of frequency. 21 pts underwent biopsy of spine lesions. Diagnostic tissue was obtained from other sites in 20 pts. Initial treatment comprised chemotherapy in 23 pts (12 MFB, 10 MS, 1 UFB), surgery in 11 pts (9 UFB, 2 MFB), radiation therapy in 6 pts (UFB) and intralesional application of steroids in 1 pt (UFB). Instabilities were stabilisized with corsets or surgical procedures. During a median observation time of 7y 1m (range 3y 3m - 11y 4m) 33/ 41 pts (80%) remained disease free after initial therapy. 2 pts (5%) had a single reactivation, 2 other pts (5%) showed 2 or more reactivations and one pt experienced a chronic course. All reactivations occured in other sites than the initial lesions. 2 pts (5%) with MS-LCH had a fatal course and 1 pt was lost to follow up. In the remaining 38 children, 5 (13%) symptomatic and 24 (63%) asymptomatic pc were present at a median of 7y 1m (range 3y 3m - 11y 4m) after diagnosis. Symptoms included episodic back-pain (4 pts) and walking-impairment (1pt). Signs included vertebra plana (13 pts), reduction in height of the vertebral body (6 pts), spondylodesis (7 pts), scoliosis (4 pts) and kyphosis (5 pts). In conclusion, involvement of the spine in LCH follows a benign course with a low rate of symptomatic pc (5/38 pts =13 %). Diagnostic and therapeutic management depends on site of the lesion and clinical presentation.

"LCH NEUROLOGICAL DISEASE" IN A 13 YEAR OLD BOY

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In the Children's Oncohaematology Clinic in Sofia, Bulgaria for a period of 20 years (1974 - 1994) of the 55 cases of LCH diagnosed in children, only one of them developed "LCH Neurological Disease" without any manifestations of diabetes insipidus. A 13 year old boy is described, with combined multiple disorder of the Central Nervous System - bilateral, symmetrical periventricular demyelinisations and cerebellar atrophy. After a 12 year long evolution of the disease with manifestations of multiple bone lesions the patient developed subacute (lasting 7 days) pancerebellar disorder with manifestations of truncal and limb ataxia, nistagmus, supplemented by a syndrome of quadriparesis, better manifested in the lower limbs. In MRI cerebellar atrophy is found, as well as bilateral symmetrical hyper intense lesions in the T2W/TSE in the white matter, periventricular, suggesting demyelinisation. The mechanisms discussed are those of disturbance of the Central Nervous System by LCH with long evolution and in particular that of the cerebellar atrophy in the direction of chronic demyelinisation of the afferent and efferent cerebellar tracts or of paraneoplastic cerebellar degeneration linked with one autoimmunity mechanism towards the cells of Purkinje.

CONGENITAL SYSTEMIC LCH. REPORT OF TWO CASES.

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Two cases of congenital systemic Langerhans cell histiocytosis diagnosted and treated in our department from June 1995 until May 1996 are described. The cases concern two neonates (one female and one male) born with necrotic lesions and skin modules. The diagnosis was confirmed by skin biopsy which showed diffuse infiltration of histiocytosis CD1 antigen and S-100 protein positive. Both babies didn't present anaemia, hepatosplenomegaly or lymphadenopathy. Hepatic and renal function were normal. In both infants skeletal survey showed no lytic lesions but chest X-rays and HR CT scan revealed diffuse mottling of both lung fields. Bone marrow aspiration showed the presence of histiocytes in a percentage greater than 10%. Both babies treated with prednisolone 1 mg/kg b.w for 3 months. The first infant 12 months old now is alive and well with resolution of skin lesions within one month from the initiation of steroids while the second is still on steroids with spectacular resolution of skin lesions since the first three weeks. We conclude that congenital LCH has to be suspected in neonates with persisting skin lesions. If the disease is systemic but without organ dysfunction treatment with steroids can be beneficial.

CUTANEOUS SELF- HEALING HISTIOCYTOSIS REPORT OF 2 CASES BELONGING TO CLASS I AND CLASE II HISTIOCYTOSIS

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CASE I CONGENITAL SELF HEALING RETICULO HISTIOCYTOSIS.

A 7 day-old boy was seen with an asymptomatic eruption present from birth, characterized by multiple reddish -brown or purplish papulonodular lesions some of them eroded and crusted,occurring all over the body mainly on the face and extremities involving palms and soles.The mucous membranes were spared.Physical radiological and laboratory examinations were normal.The lesion regressed spontaneously in 3-4 months, leaving atrophic scars

Skin biopsy showed deep dermal infiltrate with sparing of the epidermis composed primarily of densely aggregated large histiocytic cells with abundant homogeneous pink cytoplasm and lobulated bean-shaped nuclei.S-100 was positive.Birbeck granules were present

CASE 2 BENIGN CEPHALIC HISTIOCYTOSIS

A 5 month-old boy was seen with an asymptomatic eruption that began 3 months before on the face and then spreaded to involve the shoulders,arms and upper part of the trunk.characterized by multiple red-brown to yellowish papulonodular lesions, 2 to 6 mm in diameter.

The mucous membranes were spared Physical, radiological and laboratory examinations were normal.

Skin biopsy showed scattered well circumscribed upper dermal infiltrate composed primarily of hystiocytes with irregularly shaped nuclei and few lymphocytes.Foam cells, Touton giant cells and Langerhans cells were absent.Histiocytic cells were S-100 negative and CD 68 positive.

Few cases of these two kinds of histiocytosis have been reported since the original descriptions by Hashimoto-Pritzker and Gianotti et al. They involve particular areas of the skin of healthy infants In spite of belonging to different classes(I and II) these entities(Congenital Self Healing Reticulohistiocytosis and Benign Cephalic Histiocytosis) have both benign course

These entities must be taken into consideration in the clinical and histological diagnosis of histiocytic syndromes

α - INTERFERON IN MAINTENANCE THERAPY FOR LANGERHANS CELL HISTIOCYTOSIS (LCH)

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Introduction: Histiocytosis of Langerhans cell is the disease of known pathogenesis, unknown etiology and predictable course. The disease can be manifested at any age, most frequently from 1-3 years. Clinical picture varies from potentially lethal leukemia like, solitary bone like lesions, or intermediate forms with characteristic bone lesions, skin lesions, mucous membrane with different stadium of organ dysfunction. New investigations mention the clone nature of the disease. Pathohistologicaly the histiocytes CD1a+ and S-100 protein + are present. Morphologically and fenotypicaly they are similar to dendrite antigen-presented Langerhans cells (LC) found in skin and other organs. Electron microscope analysis shows the characteristic Birbeck granules in LC. Virus etiology is seriously evaluated, and some authors have confirmed that EBV, CMV and other viral genome are present in LCH tissue. The role of cytokine in pathogenesis of LCH lesions is confirmed. Preinflamatory cytokines like IL6, IL2, IL1, IL8, TNF-a, GM-CSF and LIF are found in LCH lesions. During recent years in some hematological centers, α - interferon has been successfully used in the therapy of LCH. The way of activity is not clear yet. There are few speculative theory that α INF may activate the NK cells to destroy LC.
Material and methods : Here we present three patients with disseminated form of LCH. They were treated with combination of chemotherapy (VP-16), recommended in protocol ICL 89, with fifteen cycles at intervals of three weeks between each cycle. Maintenance therapy proceeded with α- INF. The Langerhans cells were found in each patient by positive imunohistochemistry reaction on S-100 protein, and also the Bierback granules by electron microscope. We have also found in each patient the positive serological findings of CMV and EBV in high titters.
Conclusion: Our positive experience in the treatment of Langerhans cell histiocytosis in combination with chemotherapy and α interferon may be connected with effects of interferon on viral infections. The risk of relapses can be connected with disbalance in cytokine network. All three patients reached complete stabile remission.

ELEVATED ESR AND THROMBOCYTOSIS MAY BE VALUABLE MARKERS OF ACTIVE DISEASE IN LCH

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Since LCH is a disease with an unpredictable course and unpredictable reactivations and since active disease may cause life-long sequelae, an early awareness of reactivation of the disease is important in order to consider initiation/intensification of its treatment and there is, therefore, a need for easily available markers of disease activity.
MATERIAL AND METHODS: Based on biological and clinical observations, we analysed ESR and thrombocytosis as markers of disease activity in LCH. All platelet counts and ESR values were retrospectively analyzed in all children (n=27) seen at the Department of Pediatric Hematology and Oncology at the Karolinska Hospital during the period Jan 1993 - June 1996. For each child, the mean values of ESR and platelet count for each quarter of a year were calculated. Each quarter of a year was thereby represented by an ESR and a platelet count estimate for each child. Independently, the disease of each child was categorized with regard to extension (single system - single site, multifocal bone and multisystem (MS)) as well as activity (active, intermediate or resolution) for each period of time.
RESULTS: The mean of all the ESR estimates (n=77) during each quarter of a year with active disease was 21 mm, during intermediate disease activity 14 mm and during resolution 8 mm. The respective platelet counts (n=141) were 433 x10^9/L, 372 x10^9/L and 304 x10^9/L. In the active disease group 69% (11/16) had ESR values ≥15 mm and 44% (17/39) had platelet counts ≥150 x10^9/L, while the figures in the intermediate group were 16% (3/19) and 24% (10/41) and in the resolution group 5% (2/42) and 8% (5/61), respectively. In MS disease, 10/13 (77%) of the ESR estimates during active disease were ≥15 mm whereas only 1/24 (4%) during resolution. Corresponding figures for platelet count ≥450 x10^9/L were 14/32 (44%) and 0/36, respectively.
CONCLUSION: We conclude that elevated ESR and platelet count, which are easily available laboratory parameters, may be clinically valuable markers for disease activity in LCH. Our results (ESR↑ and thrombocytosis) support the view that LCH is an inflammatory disorder.

HISTIOCYTOSIS X (L.C.H.) IN TWO SIBLINGS.

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In May 1996, the second (only) child of a family referred to our clinic because of the left facial mass with some patchy, fleshy discolouration of the skin.

She is 3 years old with normal development without any abnormal history.

On physical exam: just mentioned above; soft tissue on left side over the mandibular area, spread toward the cheek without lobulation was noticed.

Paraclinical investigation: Bone, chest, X-ray; abdominal sonography and C.A.T. scan were normal. Unne specific gravity was also normal.

The biopsy of the lesion was compatible with L.C.H. But the important fact was that the parents are first cousin and their first child (boy) was diagnosed as L.C.H. in infancy with bone skin, liver involvment. But after 15 month expired because of failure of treatment.

FATAL MALIGNANT LANGERHANS CELL HISTIOCYTOSIS SECONDARY TO ATAXIA TELEANGIECTASIA.

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Ataxia teleangiektasia (AT) is an autosomal recessive genetic disease with a 1% frequency of gene carrier and a birth frequency of 1:1000 Recently the A-T gene was mapped to chromosome 11 q 22-23. The disease affects the brain and immune system. Due to a chromosomal instability with DNA repair disorder gene carriers and patients have a 500-1000 higher tendency to develop cancer than the general population.

We report a 9 year old female with AT characterized by ataxia and recurrent infections. The girl was admitted to the hospital due to fever, dyspnoe, gastroesophageal reflux and a mediastinal mass. Immunological search for CMV, EBV, HIV, Toxoplasmosis, Q-fever, Aspergillosis and Cryptococcosis was negative. In the bronchial lavage non malignant histiocytes were seen. There was no evidence for Tbc and/or atypical mycobacteria infection. Transthoracic open biopsy of the mass gave the diagnosis of malignant histocytosis. Chemotherapy with Prednisone and Cyclophosphamide could not hold on the devastating malignancy. The child expired soon afterwards due to respiratory arrest. Autopsy revealed a disseminated malignant histiocytosis affecting the thymus, the supra- and infradiaphragmatic lymph nodes with infiltration of the lungs and the esophagus.

The immunohistochemical investigation showed the following immunophenotype of the neoplatic cells: CD45+, CD 43+, CD 4+, S-100-protein +, Lysozyme -, alpha-1-Antitrypsin -. High proliferation index with nuclear staining of about 50% of the tumor cells. Birbeck granules were detected in electron microscopy. The findings support the diagnosis of a malignant tumor of the mononuclear phagocyte immunoregulatory effector system, consistent with malignant histiocytosis of Langerhans cell origin.

We present, to our knowledge, the first reported case with true malignant Langerhans cell histiocytosis occurring on the base of ataxia teleangiektasis, a primary combined immunodeficiency syndrome with increased predisposition to leukemia lymphoma mainly of T cell origin.

UNUSUAL PREMALIGNANT AND MALIGANT DISEASE IN LCH

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The purpose of this abstract is to present unusual cases of premalignant and malignant disease in LCH. I- 7 years(yrs) old girl, with 3 months (mo) of pain and lytic bone lesions. LCH was diagnosed by biopsy. After 3 mo chemotherapy (c) the lesions became disseminated with multiple fractures and biopsy was repeated showing Ewing Tumor.She received c and Radiotherapy (rt) but she died with progressive disease 8 mo after diagnosis. II-21 mo old boy, with skin inv,relapsing otitis 1 yr before , followed by bone disseminated lesions. LCH was diagnosed by biopsy. The pt received several regimens of c and rt however he presented a disseminated and relapsing disease. 4 yrs after diagnosis, he presented splenomegaly,anemia, trombocytopenia and myelofibrosis was detected by bone marrow (bm) biopsy. The pt died 3 mo later. III-5 yrs old boy; 12 mo before admission, he presented torticolis, cervical pain and a right side weakness, MRI showed a large lesion involving clivus with an important brain stem displacement. The surgery (s)resection was partial with a marked clinical improvement.The histology was consistent with LCH. He received rt; 2 mo later a pelvic lytic lesion was evident and treated by c with a good response but 8 mo later he had a limp walking with disseminated bone pains , lytic lesions with extradural inv on L1 and S1(biopsy showed LCH)and a brain stem tumor detected by MRI. C and rt were given but the pt developed quadriparesia. A decompressive s of the brain was done but he died a few days later and the histology showed anaplastic brain stem tumor. IV-3 yrs old boy, who had anemia and hepatomegaly before admission. Blast were detected on peripheral blood but bm biopsy gave the diagnosis of LCH with no other organ inv. After multiple dry taps, 35% blasts (CD 34:47%) were founded. The pt was then treated as AML. After 1 yr,the bm was infiltrated by myeloblasts(HLADR:73%) and 7 monosomy was discovered. The pt rapidly died in aplasia and sepsis. We showed cases of LCH (I,III,IV) who could be reactives to the tumors and the pt II, very heavily pretreated with c and rt producing a secondary myelofibrosis.